REMARKS

Claims 1-9 and 12-13 were pending in the present application. Claims 1-5 and 8 have been amended herein, claims 7 and 9-13 have been canceled herein, and new claims 14-29 have been added herein. Support for amended claims 7 and 9-13 and new claims 14-29 can be found throughout the specification and original claims. No new matter has been added. Upon entry of the present amendments, claims 1-6, 8, and 14-29 will be pending.

I. Claim Objections

Claim 7 is objected to because it is alleged to be drawn to the same materials as claim 6. Although Applicants respectfully disagree with the allegation, solely to expedite prosecution and without disclaimer of subject matter, claim 7 has been canceled. Accordingly, Applicants respectfully request that the objection be withdrawn.

II. The Claimed Invention is Not Obvious

Claims 1-7 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over WO 94/110165 (hereinafter, the "Harrison reference") in view of Hagiwara et al., J. Med. Chem., 1994, 37, 2090-2099 (hereinafter, the "Harigawa reference"). In particular, the Action alleges that it would be routine for the chemist to replace phenyl with naphthyl because "Harrison suggests that lipophilicity of the aryl moiety is important since numerous compounds bearing the lipophilic CF_3 group were prepared, thus naphthyl being slightly more lipophilic would have increased potency." *See* Action at page 26. Applicants respectfully disagree.

Applicants are unable to locate any portion of the Harrison reference that compares the activity of the compounds described therein or teaches or suggests that lipophilicity of the aryl moiety is important. Indeed, the Harrison reference reports that "the compounds referred to in the Examples had IC_{50} at NKIR of less than 500 nM." (Harrison reference at page 31, lines 18-20). Simply because the Harrison reference reports compounds with aryl moieties does not mean that the lipophilicity of the aryl moiety is important. Thus, the Harrison reference does not teach or suggest that lipophilicity of the aryl moiety is important.

Further, the Action's characterization of the Harigawa reference is misguided. The Harigawa reference does not teach, as the Action alleges, that substitution of naphthyl for phenyl is routine and desirable in the field of NK_1 receptor antagonists, as alleged in the Action at page 25. Although the Harigawa reference reports that naphthylalanine was more potent than phenylalanine, the Harigawa reference also reports that (6-methylnaphthyl)-alanine and (6-chloronaphthyl)-alanine were **more than ten times less potent** than phenylalanine. *See* Harigawa reference at page 2093. Further, the Harigawa reference reports that the binding assay that resulted in naphthylalanine having increased potency over phenylalanine was conducted at **4°C**, but when the assay was conducted at 25°C (i.e., room temperature), naphthylalanine was **less potent** than phenylalanine. *See Id.* Thus, the Harigawa reference does not teach or suggest that substitution of naphthyl for phenyl is routine and desirable in the field of NK_1 receptor antagonists. Accordingly, one skilled in the art would not be motivated modify the compounds reported in the Harrison reference to obtain the compounds as claimed by Applicants.

In view of the foregoing discussion, Applicants respectfully assert that the claimed invention is not obvious and request that the claim rejection be withdrawn.

III. The Claimed Invention is Enabled

Claims 7-9 and 12-13 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Action alleges that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. As a preliminary matter, claims 7, 9, 12, and 13 have been canceled herein, rendering their rejection moot. Applicants respectfully request reconsideration thereof, as applied to claim 8, because one skilled in the art would able to make and/or use the invention without undue experimentation.

The enablement requirement of § 112 is satisfied so long as a disclosure contains sufficient information that persons of ordinary skill in the art having the disclosure before them would be able to make and use the invention. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (the legal standard for enablement under §112 is whether one skilled in the art would be able to practice the invention without undue experimentation). In this respect, the following statement

from *In re Marzocchi*, is noteworthy:

> …a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must** be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling.
>
> … it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971) (emphasis added).

The Action cites Kenakin et al., TRENDS in Pharmacological Sciences, 2002, 23, 275-280 (hereinafter, the "Kenakin reference"), to support its allegation that the affinity exhibited by the claimed compounds does not correlate with therapeutic utility (Action at page 28). Applicants respectfully disagree. Applicants are unable to locate any portion of the Kenakin reference that reports a compound having affinity and no therapeutic utility. Rather, the Kenakin reference reports that compounds with affinity and no efficacy can still have therapeutic utility. The Kenakin reference presents cimetidine as an example of a drug with affinity but no efficacy (Kenakin reference at page 275). Cimetidine is indicated for, *inter alia*, the short-term treatment of active duodenal ulcer and gastroesophageal reflux disease. Thus, compounds with no efficacy can still have therapeutic utility. Accordingly, the Kenakin reference cannot support a general rule that affinity does not correlate with therapeutic utility.

The Action also asserts that Rosensweig-Lipson et al., Pharmacology & Therapeutics, 2007, 113, 134-153 (hereinafter, the "Rosensweig-Lipson reference") suggests that "the state of the art in the area of these dual antagonists is murky at best" (Action at page 29). The Action

further asserts that "even if these compounds were evaluated simply as NK_1 antagonists" that it would "be unlikely that one of skill in the art would know what to do with these compounds," based on failed trials in McLean Current Pharmaceutical Design, 2005, 11, 1529 (hereinafter, the "McLean reference") (Action at pages 29-30). Applicants respectfully disagree.

The claimed methods can be practiced without undue experimentation. As asserted by Applicants' specification, the compounds have both NK_1 antagonist and serotonin reuptake inhibitory (SRI) activity. There is ample evidence of the efficacy of NK_1 antagonists and SRI's for treating depression and anxiety. For example, the McLean article summarizes the results of **19 positive preclinical studies** showing the anxiolytic effect of NK_1 antagonists and **14 positive studies** showing the antidepressant effect of NK_1 antagonists, all published prior to the filing date of the present application (McLean, Table 2 at pages 1536-37). The anxiolytic and antidepressant effect of NK_1 antagonists is further supported by the articles cited by Applicants' specification, showing the involvement of NK_1 receptors in depression and a decrease in the anxiety behavior of mice following administration of NK_1 antagonists (Papp et al., Behav. Brain Res., 2000, 115, 19; and Santarelli et al., Proc. Nat. Acad. Sci., 2001, 98, 1912; cited in the specification at page 2, lines 1-4). Moreover, serotonin reuptake inhibitors have efficacy in treating anxiety and depression (Boerner and Moeller, Pharmacopsychiatry, 1999, 32, 119-26). Hence, there is a clear link between the treatment of depression and anxiety and NK_1 antagonist and serotonin reuptake inhibition activity. Accordingly, one of skill in the art would be able to practice the claimed invention without undue experimentation.

In light of this evidence, the sections of Rosenzwieg-Lipson and McLean references cited in the Action fail to provide sufficient evidence to doubt the enablement of the claimed invention, as amended. As to the McLean reference, the Action points to a statement in the article that "[t]o date there are three positive trials in depression, one positive trial in panic, several failed trials and at least 2 negative studies" (Action at pages 29-30; McLean at page 1542). However, in the allegedly "failed" trial for MK-869, a dose dependent decrease in depression symptoms in subjects was observed, leading the reviewers to suggest that MK-869 would actually be effective for subjects with greater depression (McLean at page 1541). In the single negative trial for MK-869, the McLean reference indicates that the report was gleaned

from the "lay press" and that "details were not available" (McLean at page 1541). Similarly, in the negative trial for L-75927, the McLean reference indicates that the response to paroxetine, which is indicated for depression, also failed to distinguish from placebo (McLean at page 1541). Further, Applicants respectfully assert that clinical trials may fail for a variety of reasons, including safety concerns which are outside the purview of the U.S. Patent and Trademark Office. *Scott v. Finney*, 34 F.3d 1058, 1063, 32 U.S.P.Q.2d 1115, 1120 (Fed. Cir. 1994). Moreover, the McLean reference does not take into account the effect of serotonin reuptake inhibitory activity.

Although the Rosenzwieg-Lipson reference summarizes the failure of one Phase III depression trial for a single NK_1 antagonist (aprepitant) administered alone, it also states that "NK-1 antagonists have been shown to potentiate the neurochemical effects of SSRIs in preclinical studies" (Action at page 29; Rosenzwieg-Lipson at page 140). Hence, the Rosenzwieg-Lipson reference supports Applicants' assertion that the claimed invention is enabled.

In view of the foregoing discussion, Applicants respectfully assert that the claimed invention meets the requirements of 35 U.S.C. § 112, first paragraph, and request that the claim rejection be withdrawn.

IV. The Claimed Invention is Supported by Ample Written Description

Claims 1-5 and 8-9 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Action bases its rejection on the allegation that the specification gives no guidance as what "in vivo hydrolysable precursors" are (Action at page 31). Although Applicants respectfully disagree with the allegation, solely to expedite prosecution and without disclaimer of subject matter, claims 1-5 and 8 have been amended herein and claim 9 has been canceled herein. In light of the amendments made herein, Applicants respectfully assert that the claimed invention meets the written description requirement and request that the claim rejection be withdrawn.

V. Obviousness-type Double-Patenting

Claims 1-9 and 12-13 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-13 of copending Application No. 10/539,140 in view of Elliot et al., Bioorganic & Medicinal Chemistry Letters, 2002, 12, 1755-1758 (hereinafter, the "Elliot reference"). The Action alleges that the instant claims differ from those of copending Application No. 10/539,140 by the identity of the moiety linking the naphthyl ring to the piperidine, and that this change is taught by the Elliot reference. The rejection is currently provisional. If the co-pending application is granted, Applicants will file the necessary disclaimer if and as appropriate.

In addition, Claims 1-9 and 12-13 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 10/525,303 in view of the Elliot reference. The Action alleges that the instant claims differ from those of copending Application No. 10/525,303 by the identity of the moiety linking the naphthyl ring to the piperidine, and that this change is taught by the Elliot reference. The rejection is currently provisional. If the co-pending application is granted, Applicants will file the necessary disclaimer if and as appropriate.

VI. Conclusion

Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (610) 640-7851 to resolve any remaining issues.

The Commissioner is hereby authorized to debit any underpayment of fee due or credit any overpayment to Deposit Account No. 50-0436.

Respectfully submitted,

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